* synthetic inhibitors of purine synthesis :

1) sulfonamide :

- work on bacteria only (not interfere with human cell function)(MCQ)
- antibiotic (not chemotherapy)
- analogs of PAPA that competitively (MCQ) inhibit bacterial synthesis of folic acid (MCQ)
-because purine synthesis requires THF as a coenzyme, the sulfa drugs slow down this pathway in bacteria .
- human cannot synthesis folic acid & must rely on external sources .

2)Trimethoprim :

- antibacterial activity (not interfere with human cell function)(MCQ)
- folate analog
-inhibit bacteria dihydrofolate reductase

3) methotrexate :

- inhibit human (MCQ) purine synthesis .
- chemotherapy (cancer by inhibiting the synthesis of nucleotide ,of DNA & RNA)
-inhibit the reduction of dihydrofolate to tetrahydrofolate , catalyzed by dihydrofolate reductase .
-toxic to all dividing cell especially { (bone marrow > anemia),(skin > scaly skin),(GIT > GIT disturbance), (immunodeficiencies),(hair follicle > baldness).

* conversion of IMP TO AMP or GMP : (MCQ)

- uses a two- step requiring energy pathway .
- AMP synthesis require GTP (MCQ)
-GMP synthesis require ATP (MCQ)
- The first reaction in each pathway is inhibited by the end product of that pathway .
* explanation : if there is enough AMP > IMP TO GMP
If there is enough GMP > IMP TO AMP

If there is enough AMP & GMP , the de nova pathway of purine synthesis is turned off at amidotransferase step .

- mycophenolic acid :

a) it is reversible uncompetitive inhibitor of IMP dehydrogenase (an enzyme used in de nova synthesis of GMP . (MCQ)

b) it prevent graft rejection by deprives T & B cells from GMP (key component of nucleic acid)

Mycophenolic acid is potent competitive inhibitor of IMP dehydrogenase. F

*Conversion of nucleoside monophosphate (NMP) to nucleoside diphosphate (NDP) & triphosphate (NTP) :

*** base specific nucleoside monophosphate kinase :**

a) convert (NMP) to (NDP)

b) do not discriminate between ribose or deoxyribose as a substrate (MCQ)

c) use ATP

d)reversible

- AMP or (dAMP) + ATP <Adenylate kinase > 2ADP

Adenylate kinase is particularly active in liver & muscle .

- GMP or (dGMP) + ATP < guanylate kinase > GDP + ADP

* Nucleoside diphosphate kinase :

a) convert (NDP) TO (NTP)

b) has broad specificity

c) use ATP

d)reversible

GDP + ATP <> GTP + ADP

CDP + ATP <> CTP + ADP

5- Both NMP- & NDP- kinases are reversible enzymes. T

Salvage pathway of purine

-Purine from diet or normal cell turnover .

* conversion of purine bases to nucleotides:

Hypoxanthine + PRPP > IMP + PPi

Guanine + PRPP > GMP + PPi

- enzyme : hypoxanthine-guanine phosphribosyltransferase(HPRT)
- use PRPP as a source of ribose 5-phosphate (MCQ)
- irreversible because of the release of pyrophosphate (MCQ)

Adenine + PRPP > AMP + PPi

- enzyme : Adenine phosphribosyltransferase (APRT)
- use PRPP as a source of ribose 5-phosphate (MCQ)
- irreversible because of the release of pyrophosphate (MCQ)

– de novo synthesis of purines requires much more energy compared to that of their salvage réactions.(T)

* lesch-Nyhan syndrome :

a) X-linked recessive inherited disorder.

b) complete deficiency of HPRT so inability to salvage hypoxanthine or guanine so produce high amount of uric acid . (MCQ) (NOT Adenine)

c) the lack of HPRT lead to :

- increase PRPP - decrease IMP & GMP (MCQ)(NOT AMP)

SO increase the de nova synthesis of purine (MCQ) because of Glutamine-phosphoribosylamidotransferse (committed step in de nova purine synthesis)

- decrease purine reutilization & increase purine production cause increase in uric acid making the syndrome a sever form of gout .
- patient has kidney stones,neurologic,selfmutation,involuntary movements .

* synthesis of deoxyribonucleotides :

Ribonucleoside diphosphate (MCQ) > deoxy Ribonucleoside diphosphate
(very important what we will said)
Enzyme : ribonucleotide reductase (MCQ)

a) multisubunit (two identical B1 & two identical B2)
b) specific for (ADP,GDP,CDP&UDP)(MCQ)(NOT TDP)
c) hydrogen donor needed for the reduction of 2-hydroxyl group are : two sulfhydryl so it forms a disulfide bond.
d) inhibitor : dATP

1) regeneration of reduced enzyme :
-The disulfide bond greaten above must be reduced in order to ribonucleoside reductase to continue his function , this will done by thioredoxin.

- thioredoxin :

a) peptide coenzyme of ribonucleoside reductase .
b)contain two cysteine residue separated by two amino acid
c)to regenerate thioredoxin we need NADPH + H (MCQ)

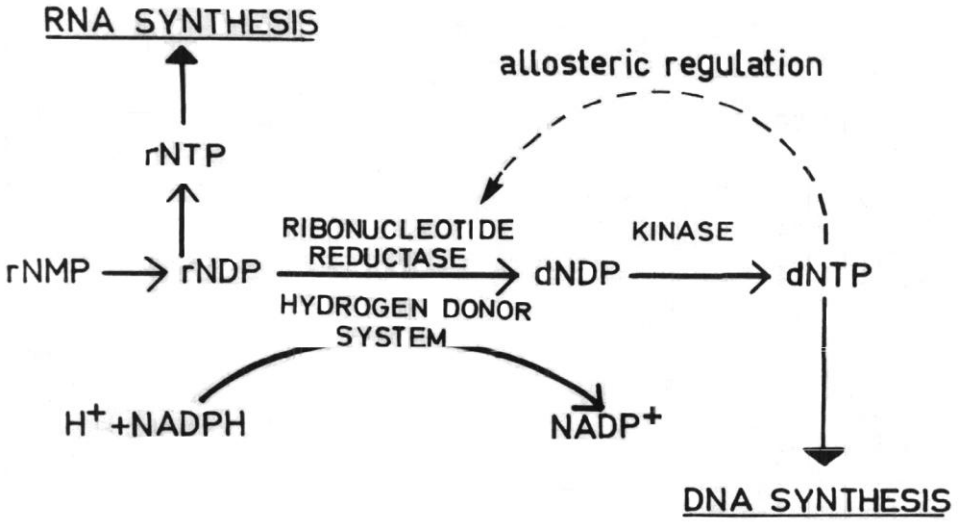
Concerning ribonucleotide reductase:
a. It converts ribonucleoside triphosphates into their deoxy-form.
b. Binding of dATP to activity site of the enzyme turns the enzyme on.
c. NADPH is the immediate donors for the hydrogen atoms needed for reduction.
d. It is one-unit enzyme that has both catalytic & regulatory regions.
e. Thioredoxin is an essential immediate in the regeneration of enzyme into its active, reduce form. (answer)

– regeneration of reduced thioredoxin requires NADH + H+. (F)

* regulation of deoxyribonucleotide synthesis :

- ribonucleotide reductase has single active site & two site involved in regulation.
-dATP is an allosteric inhibitor (MCQ)(not competitive) but ATP is an activator .
- SO dATP prevent DNA synthesis this explain its toxicity .

- Substrate specificity site :
  a) it regulate the conversion of different species of ribonucleoside to deoxyribonucleoside as they are required for DNA synthesis.
  b) (ATP , dATP , dTTP , dGTP)



تمت المحاضرة الثانية

Done by

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